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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,492	EUL, JOACHIM	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,24-57 and 64-79* is/are pending in the application.

4a) Of the above claim(s) *1-12,24-57,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on December 4, 2008.

Claims 1-12, 24-57, and 64-79 are currently pending in the instant application. Claims 1-12, 24-57, and 64-65 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 25, 2008.

Accordingly, claims 66-79 are currently under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Response to Arguments

Applicant's arguments with respect to claims 13-23 and 58-63 have been considered but are moot in view of the cancellation of the claims and new ground(s) of rejection. See below.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

Claims 66-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Puttaraju et al. (*Nature Biotechnology,* 1999, citation of record) in view of Reyes et al. (*RNA,* 1996, citation of record), Caudevilla et al. (*Nucleic Acids Research,* 2001, citation of record), and Bruzik et al. (*PNAS,* 1995, citation of record).

The claims are drawn to a DNA construct that encodes a trans-splicing RNA, wherein the DNA construct comprises nucleotide sequences encoding a replication origin, an RNA polymerase-II promoter, a polyadenylation sequence, at least one antisense sequence hybridizing with at least 18 nucleotides in the mutated exon or a flanking intron region, the 5' outron antisense sequence having a branch A site of the 8-mer sequence of "UACUAACA/G" hybridizes with the intronic polypyrimidine sequence of U and C and an AG dinucleotide at the 3' splice site and a GU dinucleotide and a 3-mer sequence of "AAG" at the 5' splice site, wherein the construct further comprises a cDNA sequence of non-mutated exon 1 and an ESE sequence, and a probe comprising said DNA construct.

Puttaraju et al. teach a trans-splicing DNA construct comprising an 18-nucleotide target binding domain sequence that is complementary to a target pre-mRNA sequence, a branch point sequence having a "UACUAAC" consensus sequence, a polypyrimidine tract sequence, and an AG dinucleoitde at the 3' splice site, wherein all sequences are cloned into pcDNA3.1,. which inherently has a polymerase II promoter and a polyadenylation signal sequence. See the attached Promega citation. They teach that the trans-splicing DNA construct is useful in RNA repair. See

the entire reference. Puttaraju et al. do not teach that the trans-splicing DNA construct comprises an GU dinucleotide at the 5' splice site, or the 5' splice site has the 6-mer sequence of "GUAAGU", or at least one ESE sequence.

Reyes et al. teach that the "GU" dinucleotide is the canonical 5' splice site recognition sequence during trans-splicing and that the 5' splice site comprises a sequence of GUAAGU. See the entire reference.

Caudevilla et al. teach that an ESE (exonic splicing enhancer) sequence induces or activates trans-splicing. See the entire reference.

Bruzik et al. teach that trans-splicing is mediated by interactions between splicing factors bound to the splicing enhancer sequence and general splicing factors bound to the 5' and 3' splice sites. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the trans-splicing DNA construct of Puttaraju et al. so that it further comprises the 5' splice site sequence of Reyes et al. and the ESE sequence of Caudevilla et al.

One of ordinary skill in the art would have been motivated to combine the trans-splicing factors of Reyes et al. and Caudevilla et al. with a reasonable expectation of success, because Bruzik et al. taught that trans-splicing is mediated by interactions between splicing factors bound to the splicing enhancer sequence and general splicing factors bound to the 5' and 3' splice sites. Hence, one of ordinary skill in the art trying to enhance the trans-splicing efficacy of the trans-splicing DNA construct capable of gene repair such as the trans-splicing DNA construct of Puttaraju et al. would have been motivated to incorporate the 5' splice site sequence as well as the ESE sequence into the trans-splicing DNA construct. Since the trans-splicing elements

claimed in the instant case were known to not only exist but also to cooperatively orchestrate the trans-splicing activity of a trans-splicing RNA at the time of the invention, and since the skills and knowledge to make the claimed trans-splicing construct were within the technical grasp of one of ordinary skill in the art as shown by Puttaraju et al., the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 66-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Puttaraju et al. (*Nature Biotechnology,* 1999, citation of record) in view of Mitchell (US 6,013,487, citation of record), Caudevilla et al. (*Nucleic Acids Research,* 2001, citation of record), and Bruzik et al. (*PNAS,* 1995, citation of record).

The claims are described above.

Puttaraju et al. teach a trans-splicing DNA construct comprising an 18-nucleotide target binding domain sequence that is complementary to a target pre-mRNA sequence, a branch point sequence having a "UACUAAC" consensus sequence, a polypyrimidine tract sequence, and an AG dinucleoitde at the 3' splice site, wherein all sequences are cloned into pcDNA3.1,. which inherently has a polymerase II promoter and a polyadenylation signal sequence. See the attached Promega citation. They teach that the trans-splicing DNA construct is useful in RNA repair. See the entire reference. Puttaraju et al. do not teach that the trans-splicing DNA construct comprises the 5' splice site sequence of "GUAAGU" or at least one ESE sequence.

Mitchell teaches a DNA construct that encodes a trans-splicing RNA, comprising a polyadenylation sequence, polypyrimidine tract, branch A site, 3' splice site comprising an AG dinucleotide and a 5' splice site comprising "GUAAGU", a 15-30 nucleotide sequence

complementary to (or in antisense orientation) the targeted region of the selected pre-mRNA including exon 1 lacking the ATG sequence, or an entire coding sequence of the pre-mRNA, which produces a therapeutic molecule in a cell when the DNA construct is introduced into the cell. See Figures 4A and 6B; columns 2, 4-7; claims 19-34. Mitchell teaches that the DNA construct that produces said therapeutic molecule in a cell is a commercially available vector pcDNA3.1(-), which comprises CMV promoter, T7 promoter, multiple cloning site, BGH polyadenylation sequence, f1 origin, neomycin resistant gene (ORF), SV40 early polyadenylation signal, pUC origin, and ampilicin resistance gene.

Caudevilla et al. teach that an ESE (exonic splicing enhancer) sequence induces or activates trans-splicing. See the entire reference.

Bruzik et al. teach that trans-splicing is mediated by interactions between splicing factors bound to the splicing enhancer sequence and general splicing factors bound to the 5' and 3' splice sites. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the trans-splicing DNA construct of Puttaraju et al. so that it further comprises the 3' and 5' splice site sequences of Mitchell and the ESE sequence of Caudevilla et al.

One of ordinary skill in the art would have been motivated to combine the trans-splicing factors of Mitchell and Caudevilla et al. with a reasonable expectation of success, because Bruzik et al. taught that trans-splicing is mediated by interactions between splicing factors bound to the splicing enhancer sequence and general splicing factors bound to the 5' and 3' splice sites. Hence, one of ordinary skill in the art trying to enhance the trans-splicing efficacy of the trans-

splicing DNA construct capable of gene repair such as the trans-splicing DNA construct of Puttaraju et al. would have been motivated to incorporate the 5' splice site sequence as well as the ESE sequence into the trans-splicing DNA construct. Since the trans-splicing elements claimed in the instant case were known to not only exist but also to cooperatively orchestrate the trans-splicing activity of a trans-splicing RNA at the time of the invention, and since the skills and knowledge to make the claimed trans-splicing construct were within the technical grasp of one of ordinary skill in the art as shown by Puttaraju et al., the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

This application contains claims 1-12, 24-57, and 64-65 drawn to inventions nonelected with traverse in the reply filed on March 25, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635